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Cerebroprotection Mediated by Angiotensin II

A Hypothesis Supported by Recent Randomized Clinical Trials

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Based on the Medical Research Council study, Brown and Brown hypothesized in 1986 that angiotensin II could protect against strokes by causing vasoconstriction of the proximal cerebral arteries, thereby preventing Charcot-Bouchard aneurysms from rupturing. In light of this hypothesis, we evaluated the cerebroprotective effects of various drug classes in recent double-blinded, prospective, randomized trials, such as SHEP, PATS, CAPPP, HOPE, PROGRESS, INSIGHT, NORDIL, LIFE, SCOPE, ANBP2, and ALLHAT. Drugs that activate the AT2 receptors, such as diuretics, calcium antagonists, and angiotensin receptor blockers (ARBs), were consistently more beneficial for stroke reduction than drugs devoid of such activation, such as beta-blockers and angiotensin-converting enzyme (ACE) inhibitors, despite an equal fall in arterial pressure (at least in patients with a low incidence of cardiac complications). These clinical and epidemiologic observations are supported by experimental data documenting greater cerebroprotection with ARBs (which increase angiotensin II levels and stimulate the AT2 receptors) than with ACE inhibitors. Stroke is the most devastating consequence of hypertensive cardiovascular disease, and our hypothesis of cerebroprotection by AT2 receptor activation should be tested by a head-to-head comparison of an ARB with an ACE inhibitor. (J Am Coll Cardiol 2004;43:1343–7) © 2004 by the American College of Cardiology Foundation

In 1986, Brown and Brown (1) put forth the provocative hypothesis that angiotensin II could have some cerebroprotective effects. The hypothesis was based on findings of the first Medical Research Council (MRC) study (2) in which, while achieving quite similar decreases in arterial pressure, diuretics reduced the relative risk of stroke 2.4 times better than beta-blockers. However, the suggestion that one of the most powerful vasoconstrictors, such as angiotensin II, deemed to be vasculotoxic, could have a protective effect in the brain seemed extremely farfetched and did not pass muster in the scientific community. Moreover, all subsequent randomized trials in hypertension, until recently, were diuretic-based and did not allow this hypothesis to be tested.

Do diuretics have a specific cerebroprotective effect? Ever since the Veterans Administration trials (3,4), we have known that antihypertensive therapy with diuretics was extremely efficacious in reducing the rate of strokes. The common clinical contention was to ascribe this stroke reduction to diuretics' powerful lowering of systolic blood pressure (SBP), as observed, for instance, in the Systolic Hypertension in the Elderly Program (SHEP) study (5). However, in most studies (2,5–13), a better stroke reduction was achieved with diuretics than with other antihypertensive drugs, such as beta-blockers and angiotensin-converting enzyme (ACE) inhibitors, despite similar reductions in blood pressure (BP) (Table 1).

The Post-stroke Antihypertensive Treatment Study (PATS) (6) and the Perindopril Protection Against Recurrent Stroke (PROGRESS) study (7) are a case in point. Although SBP was lowered to the same extent (5 mm Hg) by monotherapy with both a diuretic or ACE inhibitor, respectively, a meager 5% reduction of strokes was seen with perindopril in PROGRESS, whereas a highly significant reduction of strokes (29%) resulted with indapamide in PATS. The addition of a diuretic to an ACE inhibitor in PROGRESS resulted in a dramatic improvement in stroke reduction, from 5% to 43% for only a 7-mm Hg additional fall in SBP. According to the PROGRESS investigators, a 10-mm Hg SBP fall is expected to decrease the risk of stroke recurrence by only 28% in this population.

Diuretics in combination therapy. Not only were diuretics in monotherapy superior to other antihypertensive drugs for stroke prevention but also a similar phenomenon could be observed when the stroke risk reduction against placebo was compared between diuretic monotherapy and combination therapy. In both MRC studies (2,8), stroke prevention was the lowest with beta-blocker monotherapy and the highest with diuretic monotherapy. Whenever a beta-blocker was added to the diuretic, the efficacy diminished. In the SHEP study (14), patients receiving a combination of a beta-blocker with a diuretic had a 34% higher risk of stroke than those receiving diuretic monotherapy, despite equal BP control. In the study by Klungel et al. (15), all

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Abbreviations and Acronyms

ACE	= angiotensin-converting enzyme
ALLHAT	= Antihypertensive and Lipid-Lowering treatment to prevent Heart Attack Trial
ANBP2	= Second Australian National Blood Pressure study
ARB	= angiotensin II receptor blocker
BP	= blood pressure
CAPPP	= CAPtopril Prevention Project
HOPE	= Heart Outcomes Prevention Evaluation study
INSIGHT	= International Nifedipine-GITS Study: Intervention as a Goal in Hypertension Treatment
LIFE	= Losartan Intervention For Endpoint study
MRC	= Medical Research Council
NORDIL	= NORdic DILtiazem study
PATS	= Post-stroke Antihypertensive Treatment Study
PROGRESS	= Perindopril Protection Against Recurrent Stroke
SBP	= systolic blood pressure
SCOPE	= Study on COgnition and Prognosis in the Elderly study
SHEP	= Systolic Hypertension in the Elderly Program

thiazide combinations (beta-blocker, calcium antagonist, ACE inhibitors) decreased the stroke risk more than non-thiazide combinations. With thiazide monotherapy, the stroke risk was more than twice lower than that with a non-thiazide combination.

Beta-blockers. Beta-blockers in monotherapy or in combination are remarkably ineffective in reducing the risk of stroke. In the MRC study of the elderly (8), despite the fall in BP, strokes were not significantly reduced by atenolol-based therapy compared with placebo. Similarly, in the Dutch Transient Ischemic Attack (TIA) trial (16) of patients with manifest cerebrovascular disease, atenolol, despite lowering BP, reduced the risk of stroke no better than placebo. Finally, in the Scandinavian trial (17), no cerebroprotective effects of atenolol were documented. Thus, three independent trials failed to document any benefits of beta-blockade with regard to stroke reduction, despite a significant fall in BP.

Calcium antagonists. Ever since the Systolic Hypertension in Europe (Syst-Eur) trial (18), calcium antagonists have been known to reduce stroke rates. When the cerebroprotective effects of diuretics were compared with long-acting dihydropyridine calcium antagonists, there seemed to be little, if any, difference. In the International Nifedipine-GITS Study: Intervention as a Goal in Hypertension Treatment (INSIGHT) study (19), in which BP was lowered to the same extent in both treatment arms, the reduction of strokes with the nifedipine was slightly though not significantly better. In the Antihypertensive and Lipid-Lowering treatment to prevent Heart Attack Trial (ALLHAT) (11,13), the best stroke reduction was achieved by amlodipine. Chlorthalidone was not significantly inferior to amlodipine, but patients taking lisinopril and doxazosin did significantly worse. In the European Lacidipine Study on Atherosclerosis (ELSA) study (20), the long-acting dihydropyridine lacidipine, compared with atenolol, decreased the risk of stroke by 36%, but this decrease failed to reach significance because of the low power (only 23 strokes were observed). In the NORdic DILtiazem (NORDIL) study (21), even though BP was lowered somewhat less, 20% greater cerebroprotection was achieved by diltiazem than by conventional therapy (diuretics and beta-blockers). Prospective studies (13,19–22) that compared calcium antagonists and diuretics with regard to stroke outcome are shown in Table 2.

Angiotensin II receptor blockers (ARBs). In the Losartan Intervention For Endpoint (LIFE) study (23) of hypertensive patients with left ventricular hypertrophy, losartan reduced the risk of stroke better than atenolol. The difference was particularly pronounced in patients with isolated systolic hypertension (24), where losartan achieved an impressive 40% stroke reduction. In the Study on Cognition and Prognosis in the Elderly (SCOPE), candesartan reduced the non-fatal stroke rate by 28% compared with the control group (12). However, there was a 3.2/1.6-mm Hg difference in BP, favoring candesartan. In the subgroup with isolated systolic hypertension, the benefits of ARBs were even more pronounced. The recent publication of the Acute Candesartan Cilexetil Therapy in Stroke Survivors (ACCESS) pilot trial (25) further supports the BP-independent cerebroprotective effect of ARBs.

Angiotensin-converting enzyme inhibitors. As discussed earlier, in PROGRESS (7) and ALLHAT (11,13), ACE inhibitors were not very efficacious in reducing the risk of stroke. The same is true for CAPtopril Prevention Project (CAPPP) trial (9), in which captopril was even associated with a 43% greater stroke risk in the on-treatment analysis compared with conventional treatment based on thiazides and/or beta-blockers; however, SBP was 3 mm Hg higher in the captopril arm. The exception to the rule seems to be the Heart Outcomes Prevention Evaluation (HOPE) study (10), in which a 32% reduction of strokes was documented in patients taking ramipril compared with those receiving placebo. We should consider, however, that the HOPE study population was unique in that all patients had vascular disease and more than 80% had coronary heart disease. Not surprising, the incidence of cardiac complications, such as myocardial infarction and heart failure, exceeded that of stroke by five-fold. Cardiac complications are a well-known risk factor for strokes (26). However, although strokes in uncomplicated hypertension are most often lacunar or hemorrhagic and closely related to small cerebral arterial disease (27), strokes associated with heart and large-vessel disease are most often embolic or related to plaque destabilization. Because ramipril in the HOPE study prevented three times more cardiac events than strokes, it is very likely

Table 1. Prospective Studies Showing Superior Stroke Protection by Diuretics Compared With Placebo or Other Antihypertensive Treatment

Study (Reference No.)	Year	No. of Patients	Type of Patients	Follow-Up (yrs)	Comparative Treatments	Stroke Outcome
MRC (2)	1985	17,354	Hypertensive	5.5	Bendrofluazide vs. placebo and propranolol vs. placebo	Diuretics reduced stroke rate by 70%. Beta-blockers reduced stroke rate by only 27%; this reduction was non-significant in smokers.
SHEP (5)	1991	4,736	ISH in elderly	4.5	Chlorthalidone vs. placebo	Diuretics reduced stroke rate by 36%.
MRC (8)	1992	4,396	Elderly and hypertensive	5.8	Hydrochlorothiazide/amiloride vs. placebo and atenolol vs. placebo	Diuretics reduced stroke rate by 33%. Beta-blockers reduced stroke by a non-significant 18%.
PATS (6)	1995	5,665	Post-stroke	3	Indapamide vs. placebo	Diuretics reduced stroke rate by 29%.
CAPPP (9)	1999	10,985	Hypertensive	6.1	Captopril vs. diuretics or beta-blockers or other	The rate of stroke was higher with captopril: by 25% in the intention-to-treat analysis and by 43% in the on-treatment analysis, whereas systolic BP was 3 mm Hg higher.
HOPE (10)	2000	9,297	80% with coronary heart disease	1.5	Ramipril vs. placebo	Total stroke risk reduction of 32%, with a 3-mm Hg lower systolic BP.
ALLHAT (11)	2000	24,335	Hypertensive, 25% with coronary heart disease	4	Doxazosin vs. chlorthalidone	Higher stroke risk of 19% with doxazosin, with 2-mm Hg higher systolic BP.
PROGRESS (7)	2001	6,105	Post-stroke	4	Perindopril vs. placebo and perindopril plus indapamide vs. placebo	The rate of stroke was not reduced by an ACE inhibitor but was significantly reduced by 43% with combination therapy of ACE inhibitor and diuretics.
SCOPE (12)	2002	4,937	Hypertensive and elderly	5	Candesartan vs. other antihypertensives	Reduction in nonfatal strokes of 28% with candesartan, with 3.2/1.6-mm Hg BP difference.
ALLHAT (13)	2002	24,309	Hypertensive	4.9	Lisinoprol vs. chlorthalidone	Higher stroke rate of 15% with lisinopril ($p < 0.02$); no difference in whites and 30% difference in blacks.

ACE = angiotensin-converting enzyme; ALLHAT = Antihypertensive and Lipid-Lowering treatment to prevent Heart Attack Trial; BP = blood pressure; CAPPP = CAPtopril Prevention Project; HOPE = Heart Outcome Prevention Evaluation; ISH = isolated systolic hypertension; MRC = Medical Research Council; PATS = Post-stroke Antihypertensive Treatment Study; PROGRESS = Perindopril Protection Against Recurrent Stroke Study; SCOPE = Study on Cognition and Prognosis in the Elderly; SHEP = Systolic Hypertension in the Elderly Program.

that it diminished the stroke risk predominantly by reducing cardiac complications and preventing plaque destabilization (28–30). This indirect stroke prevention by reducing cardiac complications may also mitigate the superiority of angiotensin II-increasing drugs, like thiazides or dihydropyridine, in stroke prevention, compared with ACE inhibitors, as observed in the non-black populations of ALLHAT (11,13) and the Second Australian National Blood Pressure

Table 2. Prospective Studies Comparing Calcium Antagonists and Diuretics

Study (Reference No.)	Year	No. of Patients	Type of Patients	Follow-Up (yrs)	Comparative Treatments	Stroke Outcome
INSIGHT (19)	2000	6,321	Hypertensive	4	Nifedipine GITS vs. co-amilozide	Total stroke risk was non-significantly reduced by 10% with nifedipine.
NORDIL (21)	2000	10,881	Hypertensive	7	Short-acting diltiazem vs. beta-blockers and/or thiazide	Total stroke risk was significantly reduced by 20% with diltiazem, despite a 3-mm Hg higher systolic BP.
ELSA (20)	2002	2,334	Hypertensive	4	Long-acting lacidipine vs. atenolol	Total stroke risk was reduced by 36% with lacidipine; BP reduction was comparable.
ALLHAT (13)	2002	24,303	Hypertensive	4.9	Chlorthalidone vs. amlodipine	Non-significant 7% lower stroke risk with amlodipine for 1-mg higher systolic BP but 0.8-mm Hg lower diastolic BP.
CONVINCE (22)	2003	16,602	Hypertensive	3	Long-acting COER-verapamil vs. thiazide and/or beta-blocker	Relative risk of stroke was 1.5 (95% CI 0.90–1.48) with COER-verapamil.

ALLHAT = Antihypertensive and Lipid-Lowering treatment to prevent Heart Attack Trial; BP = blood pressure; COER = controlled-onset extended-release; CONVINCE = Controlled ONset Verapamil Investigation of Cardiovascular Endpoints; ELSA = European Lacidipine Study on Atherosclerosis; GITS = gastrointestinal therapeutic system; INSIGHT = International Nifedipine-GITS Study: Intervention as a Goal in Hypertension Treatment; NORDIL = NORdic DILtiazem study.

(ANBP2) study (31), in which the ratio of cardiac events to strokes was 3.4 and 2.35, respectively.

Unifying hypothesis. Our brief review seems to indicate that even though they lower BP to a similar extent, not all antihypertensive drug classes are equal in their cerebroprotective effect. This seems to hold true in hypertensive patients with a low incidence of coronary artery disease, such as in CAPPP, PATS, and PROGRESS. Specifically, diuretics, calcium antagonists, and ARBs, which increase angiotensin II formation (by stimulating renin secretion through sodium depletion [32], sympathetic activation [33,34], or blunting of the negative feedback [32], respectively) seem to have an edge over ACE inhibitors and beta-blockers, which decrease angiotensin II formation. The contrast between these drug classes that have an opposite effect on angiotensin II formation seems to be particularly important in low-renin populations, such as in hypertensive African Americans (32), in whom in ALLHAT (11,13) the stroke risk with lisinopril was 40% higher than that with chlorthalidone, which is unlikely to be related to the 4-mm Hg difference in SBP. In their hypothesis, Brown and Brown (1) suggested that the vasoconstrictive effect of angiotensin II in the proximal cerebral arteries could prevent Charcot-Bouchard aneurysms from rupturing. However, this AT1 receptor-mediated vasoconstrictive effect could only explain prevention of hemorrhagic but not ischemic strokes. To explain the reduction in ischemic strokes, which are far more prevalent, we further postulate that activation of the AT2 receptors by drugs that generate elevated levels of angiotensin II facilitates the recruitment of collateral vessels and increases neuronal resistance to anoxia.

Experimental evidence. A non-hemodynamic neuroprotective effect mediated by the AT2 receptor was recently suggested by Dai et al. (35) and Blume et al. (36). They showed that intracerebral administration of low doses of irbesartan (not interfering with the systemic effects of angiotensin II) before induction of experimental brain ischemia in the rat improved the neurologic outcome (35), whereas the co-administration of an AT2 receptor blocker prevented such an improvement (36). Furthermore, activation of the vascular AT2 receptor has been shown to induce vasodilation by local synthesis of nitric oxide and prostacyclin (37). Because AT2 receptors are over-expressed in the ischemic brain (38), this mechanism would increase the collateral circulation to the insulted regions. In contrast, the systemic increase of bradykinin (39) is more likely to promote vasodilation also to non-ischemic areas, thereby possibly leading to a steal syndrome. The significance of these hemodynamic mechanisms was demonstrated by two independent teams (40,41) using the experimental model of acute stroke by carotid ligation in the gerbil. At a comparable BP reduction, the gerbils had a lower mortality after preadministration of an ARB than after preadministration of an ACE inhibitor. However, when an ACE inhibitor was co-administrated with an ARB, no reduction in mortality was observed. Furthermore, when angiotensin II was intravenously infused shortly after carotid ligation, the mortality of gerbils decreased compared with controls receiving saline infusion or an isohypertensive dose of metaraminol (42), and this better outcome was associated with a more rapid partial recovery of ipsilateral cerebral blood flow (43). These experimental data indicate that ARBs, at least theoretically, offer double protection in that they inhibit the AT1 receptor-mediated pro-atherothrombotic effects and enhance the AT2 receptor-mediated protection against ischemia by increasing the generation of angiotensin II. In contrast, the benefits of ACE inhibitors in blunting the AT1-mediated pro-atherothrombotic effects might be mitigated by reducing circulating angiotensin II levels and thereby AT2 receptor-dependent cerebroprotection.

Conclusions. Recent trials have documented better stroke protection with diuretics, calcium antagonists, and ARBs compared with ACE inhibitors and beta-blockers. Clinical and experimental observations support the concept that this reduction of strokes may be mediated by AT2 receptors in small cerebral arteries. For any given fall in arterial pressure, drugs that activate these receptors have been shown to be more beneficial than drugs that are devoid of such activation (at least in patients with a low incidence of cardiac complications). As with all hypotheses, the Emmenthal cheese principle applies—it looks good, it smells good, it tastes good, but it has large holes! However, stroke is the most devastating consequence of hypertensive cardiovascular disease, and its prevention is the foremost goal of antihypertensive therapy. Our hypothesis of cerebroprotection by AT2 receptor activation should be thoroughly tested by a head-to-head comparison of an ARB and an ACE inhibitor in a patient population at high risk of cerebrovascular disease.

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